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Contents

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REVIEW

- 757 Liver immunology and herbal treatment
Balaban YH, Aka C, Koca-Caliskan U

MINIREVIEWS

- 771 Risk factors and outcomes associated with alcohol relapse after liver transplantation
Lim J, Curry MP, Sundaram V

ORIGINAL ARTICLE

Basic Study

- 781 Angiotensin II or epinephrine hemodynamic and metabolic responses in the liver of L-NAME induced hypertension and spontaneous hypertensive rats
Kimura DC, Nagaoka MR, Borges DR, Kouyoumdjian M

Retrospective Study

- 791 Use of aspartate aminotransferase to platelet ratio to reduce the need for FibroScan in the evaluation of liver fibrosis
Wong S, Huynh D, Zhang F, Nguyen NQ

ABOUT COVER

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WJH covers topics concerning liver biology/pathology, cirrhosis and its complications, liver fibrosis, liver failure, portal hypertension, hepatitis B and C and inflammatory disorders, steatohepatitis and metabolic liver disease, hepatocellular carcinoma, biliary tract disease, autoimmune disease, cholestatic and biliary disease, transplantation, genetics, epidemiology, microbiology, molecular and cell biology, nutrition, geriatric and pediatric hepatology, diagnosis and screening, endoscopy, imaging, and advanced technology. Priority publication will be given to articles concerning diagnosis and treatment of hepatology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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World Journal of Hepatology
Baishideng Publishing Group Inc
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Basic Study

Angiotensin II or epinephrine hemodynamic and metabolic responses in the liver of L-NAME induced hypertension and spontaneous hypertensive rats

Debora Conte Kimura, Marcia Regina Nagaoka, Durval Rosa Borges, Maria Kouyoumdjian

Debora Conte Kimura, Maria Kouyoumdjian, Department of Biochemistry, Federal University of São Paulo, Experimental Hepatology Laboratory, São Paulo 04023-900, Brazil

Marcia Regina Nagaoka, Department of Biosciences, Federal University of São Paulo, Experimental Hepatology Laboratory, Santos 11015-020, Brazil

Durval Rosa Borges, Department of Medicine, Federal University of São Paulo, Experimental Hepatology Laboratory, São Paulo 04023-900, Brazil

Author contributions: Kimura DC contributed to the study in the areas of data acquisition, analysis, and interpretation, as well as revision and final approval of the paper; Borges DR made substantial contributions to the study; Nagaoka MR and Kouyoumdjian M contributed to study conception and design, analysis and interpretation, and paper preparation, revision, and final approval; all authors read and approved the final manuscript.

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Correspondence to: Maria Kouyoumdjian, PhD, Associate Professor of Biochemistry, Department of Biochemistry, Federal University of São Paulo, Experimental Hepatology Laboratory, Rua Botucatu 862 (Edifício José Leal Prado), São Paulo 04023-900, Brazil. mariak.bioq@epm.br
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Abstract

AIM

To study hepatic vasoconstriction and glucose release induced by angiotensin (Ang) II or Epi in rats with pharmacological hypertension and spontaneously hypertensive rat (SHR).

METHODS

Isolated liver perfusion was performed following portal vein and vena cava cannulation; Ang II or epinephrine (Epi) was injected *in bolus* and portal pressure monitored; glucose release was measured in perfusate aliquots.

RESULTS

The portal hypertensive response (PHR) and the glucose release induced by Ang II of L-NAME were similar to normal rats (WIS). On the other hand, the PHR induced

by Epi in L-NAME was higher whereas the glucose release was lower compared to WIS. Despite the similar glycogen content, glucose release induced by Ang II was lower in SHR compared to Wistar-Kyoto rats although both PHR and glucose release induced by Epi in were similar.

CONCLUSION

Ang II and Epi responses are altered in different ways in these hypertension models. Our results suggest that inhibition of NO production seems to be involved in the hepatic effects induced by Epi but not by Ang II; the diminished glucose release induced by Ang II in SHR is not related to glycogen content.

Key words: Epinephrine; Liver perfusion; Spontaneously hypertensive rat; Glucose; Angiotensin II; L-NAME

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Core tip: Angiotensin (Ang) II and epinephrine (Epi) induce hemodynamic and metabolic responses in a normal liver. These responses are altered in different ways in two models of hypertension. We observed that inhibition of NO production seems to be involved in the hepatic hemodynamic and metabolic effects induced by Epi but not by Ang II. Furthermore, diminished glucose release induced by Ang II in spontaneously hypertensive rat is not related to glycogen content, but might be due to the glycogen phosphorylase activation by Ang II.

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INTRODUCTION

The renin-angiotensin-aldosterone system (RAAS) regulates blood pressure homeostasis and vascular injury and repair responses. This system has been associated with diverse physiological functions, but also with inflammation, fibrosis, and target-organ damage. Local forms of the RAAS have been described in many tissues^[1-5]. The importance of RAAS in the pathophysiology of hypertension has been observed in brain, heart, adrenal glands, vasculature, and kidney^[6-9].

Several components of RAAS are present in the liver, which synthesizes angiotensinogen, a glycoprotein that contains the sequence of angiotensin in its amino-terminal portion. Angiotensin converting enzyme (ACE) is a carboxypeptidase present primarily in the perivenous region. Besides converting angiotensin (Ang) I in Ang II, it is the major kininase involved in bradykinin degradation in the liver^[10]. In 1976, Borges *et al.*^[11] showed that both Ang I and Ang II infused into the portal vein of a rat

induced hypertensive effect, and they also demonstrated for the first time the conversion of Ang I into Ang II by the rat liver. This hypertensive response induced by Ang II is mediated by AT1 receptor because when losartan was co-infused with Ang II into the liver portal vein it abolished the hypertension response^[12]. Captopril infusion prevented pressor action of Ang I, thus the PHR previously attributed to Ang I is actually a result of its conversion to Ang II by hepatic ACE. This conversion is rapid, but the portal hypertensive action after Ang I *in bolus* injection is significantly delayed compared to Ang II injection^[13]. Metabolic effects induced by Ang II, such as glucose release and O₂ consumption, are only diminished in the presence of losartan, which demonstrates that these effects are partially dissociated on bivascular liver perfusion. Therefore, another receptor besides AT1R might also be involved on these Ang II hepatic effects^[12,14].

ACE inhibition or blockade of angiotensin receptors are widely used in clinical medicine in the treatment of hypertension. The role of the hepatic RAAS has been associated with fibrosis and cirrhosis, and its resulting portal hypertension. Up-regulation of hepatic ACE, ACE2 and AT1R was observed in animal models of fibrosis and cirrhosis by bile duct ligation or carbon tetrachloride induction^[15-17]. Ang II, *via* AT1R, stimulates activation of quiescent stellate cells, activates myofibroblasts proliferation, and promotes the release of inflammatory cytokines, as well as the excessive deposition of extracellular matrix components^[18].

The catecholaminergic sympathetic nervous system is another common system with metabolic (glucose and lactate release as well as oxygen consumption increase) and hemodynamic (vasoconstriction) effects. This system plays a key role in blood pressure homeostasis and normal metabolism and participates in the pathophysiology of many diseases. The liver contains abundant sympathetic innervation derived from the hepatic nerve plexus, and circulating catecholamines regulate liver tone^[19]. The presence of the α 1- and β -adrenergic receptors on hepatocytes was demonstrated in various species like catfish, goldfish, and rats^[20-22]. In fed state, epinephrine (Epi) promotes hepatic glucose production by activation of glycogenolysis and, in fasted state, Epi accelerates gluconeogenesis^[23].

In patients with essential hypertension, plasma levels of norepinephrine are significantly elevated and the increased sympathetic activity is accompanied by diastolic and systolic pressure increases. Neuroadrenergic factors may contribute to the maintenance and progression of hypertensive state as well as its development^[24]. A correlation between the RAAS and the sympathetic nervous system has also been described. The latter is activated by Ang II and plays a fundamental role in the homeostasis of blood pressure control^[25]. The multifactorial etiology of hypertension has led researchers to postulate, over time, various experimental models, each one involving one or more mechanisms, contributing to the assembly of a human essential hypertension "mosaic". A pharmacological hypertension model is the blockade

of nitric oxide synthesis. Biancardi *et al.*^[26] showed that vasoconstriction in response to L-NAME by the sympathetic tone plays an important role in the initiation and maintenance of hypertension. The RAAS also contributes to high blood pressure in animals chronically treated with L-NAME. Chronic treatment with ACE inhibitors or AT1 blockers is able to prevent the onset of, or reverse, a hypertension and renal injury already established, indicating a involvement of RAAS in the genesis and maintenance of this hypertension^[27]. A spontaneously hypertensive rat (SHR) is the widely used genetic hypertension model that presents elevated sympathetic activity^[28]. Although these animals are generally considered to be characterized by a low activity of circulating RAAS^[29], some studies indicate that treatment with ACE inhibitors or AT1 receptor blockers or both reduces cardiac or renal dysfunction or both of these dysfunctions in SHRs^[30-32].

Although the liver is not a target organ in physiopathology of hypertension, the presence of AT1 receptor and ACE may still indicate unknown specific roles. Sympathetic hyperactivity was described in most models of hypertension^[28] but little is known about the consequences of this hyperactivity in the liver. Therefore, the aim of this work was to evaluate the hepatic response to Ang II and Epi in hypertension models. Using the isolated rat liver perfusion, we studied the vasoconstrictor hepatic effect as well as metabolic (glucose release) effect of Ang II and Epi in two different hypertension experimental models: One genetic (SHR) and one pharmacological (systemic inhibition of NO synthase).

MATERIALS AND METHODS

Animals

Adult male Wistar EPM-1 rats (WIS), SHRs (bred by the Central Animal House of the Federal University of São Paulo - UNIFESP), and Wistar Kyoto (WKY) rats (bred by Central House of the University of de São Paulo - USP) aged 12-16 wk were used. The animals were housed in a conditioned environment and were fed a standard laboratory diet (Purina) and water *ad libitum*. This study was conducted according to the International Guiding Principles for Biomedical Research Involving Animals^[33] and was approved by the Ethics in Research Committee of UNIFESP (CEP 1455/09).

Experimental groups

After one week of acclimatization, two experimental groups were studied: (1) L-NAME, pharmacologic induced model of hypertension: Wistar EPM-1 rats received N^G-nitro-L-arginine methylester (0.5 mg/mL) in drinking water for 10 d and were compared to healthy, Wistar EPM-1 rats; and (2) SHRs were compared to WKY rats.

Indirect systolic blood pressure

Body weight and tail indirect systolic blood pressure (SBP) were recorded weekly. SBP was measured by tail-

cuff plethysmography (NIBP Controller, ADInstruments, Australia) in unanesthetized rats that were placed in a warm cupboard (45 °C) for 15 min. SBP values for individual rats were obtained from the average of 3-4 consecutive measurements and were considered valid only when these readings did not differ by more than 5 mmHg. Procedure was performed at least 48 h before the perfusion experiments to minimize the influence of animal stress on our results. Upon confirmation of animal hypertension, perfusion of rat liver *in situ* was conducted as previously described^[34].

Glycemia and insulinemia

Blood samples were collected from the abdominal aorta before portal vein cannulation. They were centrifuged at 3000 rpm to remove red cells, and serum was stored at -20 °C. Glucose was determined by enzymatic method (Glucose PAP kit, Labtest Diagnóstica, São Paulo, Brazil) and the concentration of insulin was determined using a direct ELISA kit specific for rat and mouse analysis (Millipore, United States).

In situ rat liver perfusion

Monovascular rat liver perfusion was performed as previously described^[34]. Briefly, the rat was anesthetized with urethane, 1.3 g/kg, *i.p.* (Sigma Chemical Co., United States), and hemoglobin-free, nonrecirculating liver perfusion was performed. Abdominal and thoracic cavities were opened and the portal vein (entry *via*) and the vena cava (exit *via*) cannulated. The perfusion fluid was Krebs/Henseleit-bicarbonate buffer, pH 7.4, containing 1 mg/mL BSA (Sigma Chemical Co., United States) saturated with an oxygen/carbon dioxide mixture (95/5%). Fluid was pumped in a constant flow (3-4 mL/min.g liver) through a temperature-regulated membrane oxygenator (37 °C) prior to entering the liver *via* the portal vein. The oxygen uptake in the outflowing perfusate was monitored continuously with a polarographic type of probe (Delta OHM HD2109.2, Italy) adequately positioned in a chamber at the exit of the perfusate. Liver viability was evaluated by bile production and oxygen consumption. The portal pressure was measured by using a vertically positioned, graduated fluid-filled column attached before the afferent cannula open to the atmospheric. After 20 min of stabilization previously determined (glucose release and portal pressure), 2 nmol Ang II (Sigma Chemical Co., United States) or 40 nmol Epi (Sigma Chemical Co., United States) was injected *in bolus* into the portal vein cannula. Aliquots of perfusate were collected (0 and every 30 s until 5 min and 6, 8 and 10 min) for glucose determination.

Portal pressure

Portal pressure was recorded during all experiments (0, 15, 30 and 45 s and 1-10 min). The portal pressure increase was determined over the basal pressure and the maximum increase measured. The portal hypertensive response (PHR; the area under the curve) was calculated

Table 1 Serum parameters and glycogen content

Group	Glycemia (mg/dL)	<i>n</i>	Insulinemia (ng/mL)	<i>n</i>	Glycogen content (mg/100 mg liver)	<i>n</i>
WIS	75.4 ± 4.2	9	2.1 ± 0.4	12	2.9 ± 0.2	10
L-NAME	80.7 ± 7.5	8	2.0 ± 0.4	12	2.3 ± 0.2	10
WKY	76.9 ± 4.0	9	3.8 ± 0.6	12	2.8 ± 0.2	10
SHR	86.2 ± 4.0	8	2.7 ± 0.4	13	2.8 ± 0.2	10

Serum and liver fragment for glycogen content measurement were collected before the liver perfusion experiment. Values are expressed as mean ± SEM. Student's *t*-test; L-NAME *vs* WIS and SHR *vs* WKY. WIS: Similar to normal rats; SHR: Spontaneously hypertensive rat; WKY: Wistar Kyoto.

from the graphic: Portal pressure increase *vs* time after agonist injection and expressed as cmH₂O.min.

Metabolic effects

Metabolic effects were evaluated on the basis of oxygen consumption and glucose release by perfused liver. Oxygen consumption was calculated from input-output differences expressed as μmol O₂ consumed/min.g liver. Glucose released was determined in perfusate aliquots using an enzymatic method (Glucose PAP kit, Labtest Diagnóstica, Sao Paulo, Brazil) and expressed as μmol glucose released/min.g liver. This parameter was also used to assure the liver viability. The amount of glucose released was calculated (area under the curve) from the graphic: Glucose increase *vs* time after agonist injection and expressed as μmol/min.g liver.

Glycogen

In order to avoid loss of the liver glycogen content during the 30 min of perfusion, a fragment of caudate lobe was removed after a rapid exsanguination at the beginning of the perfusion procedure. Quantification of the glycogen was based on the extraction of the polysaccharide with an alkaline solution (30% KOH) and its conversion into glucose during the reaction of the exergonic homogenized with a solution of sulfuric acid and anthrone^[35]. The concentration of glycogen (expressed as mg/100 mg liver) was determined from a glucose standard curve. Furthermore, liver fragments were removed at the end of the experiment and processed by the company Histotech Teaching Blades (<http://www.histotech.com.br/site/>). The histological analysis of liver glycogen was performed using the periodic acid-Schiff (PAS) staining.

Statistical analysis

The results are expressed as mean ± SEM. Comparisons were performed by using Student's *t*-test and a value of *P* < 0.05 was adopted as the level of significance. Analysis was performed using Graph Pad Prism 5.0 program.

RESULTS

Hypertension animal model characterization

Arterial blood pressure of SHR and rats submitted to drug hypertension (L-NAME) was evaluated before the perfusion experiments. The tail systolic blood pressure (mmHg) of L-NAME (169.1 ± 4.8; *n* = 12) and SHR groups (180.2 ± 5.9; *n* = 10) were higher (*t*-test, *P* <

0.001) when compared to WIS (126.4 ± 2.9; *n* = 9) and Wistar Kyoto (127.0 ± 2.0; *n* = 15), respectively. The glycemia and insulinemia of the rats used in the experiments are shown in Table 1; values of glycemia of normotensive animals were taken as the reference value. The glycemia of both the L-NAME and SHR groups was similar when compared to their respective control groups. The insulinemia of all groups were within normal range (0-118 pmol/L)^[36] without difference between groups.

The perfusion experiments were performed in the morning when the animals, which have nocturnal habits, were in a well-fed state confirmed by hepatic glycogen content. No difference in liver glycogen content among groups (Table 1) was found. At the end of perfusion another fragment of the liver was removed for histological analysis for glycogen content (PAS staining) and compared to the perfused livers of animals left for 24 h of fasting. We observed that even after 30 min of perfusion, the hepatic glycogen of all groups was noticeably higher than in fasted animals (Figure 1).

Liver viability

To ensure liver viability during the period of liver perfusion experiment (approximately 30 min), bile production and oxygen consumption were monitored. The bile was collected before and after injection of Epi or Ang II. As the bile production before and after agonist injection were similar, the arithmetic average was used for statistical analysis. The bile production (mL/min.g liver) was similar among groups (WIS: 1.2 ± 0.1, *n* = 16; L-NAME: 1.2 ± 0.1, *n* = 15; WKY: 1.1 ± 0.1, *n* = 14; SHR: 1.1 ± 0.1, *n* = 13). The oxygen consumption was observed throughout the perfusion period ensuring the functioning of the organ. The basal oxygen consumption (μmol/min.g liver) of SHR (2.5 ± 0.1, *n* = 14) was lower (*t*-test, *P* = 0.0151) when compared to WKY (3.2 ± 0.2, *n* = 16). This parameter on L-NAME (3.1 ± 0.2, *n* = 15) was similar to WIS (3.2 ± 0.1; *n* = 17). After agonist injection, oxygen consumption was maintained but no standard response was observed: It remained the same in some experiments and increased in others. As the perfusion fluid did not contain glucose, its release was observed from the beginning of the experiment. Basal glucose release was similar in all groups (Figure 2A and B); after agonists injection its release continued throughout the entire experiment, ensuring hepatic viability.

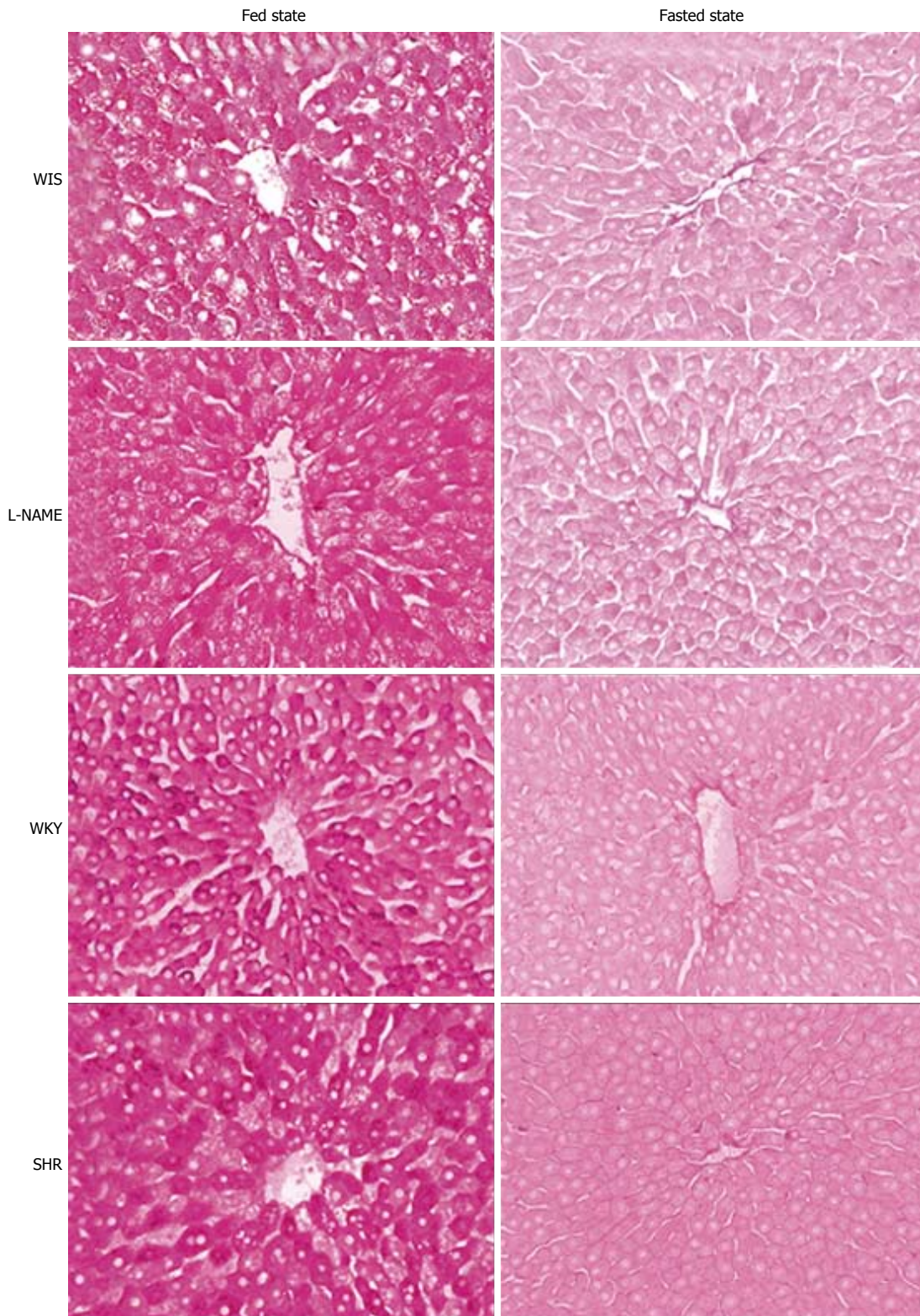


Figure 1 Hepatic glycogen. Periodic acid Schiff's staining of cross-section of perfused livers from fed or 12 h fasted rats. Fragments taken after 30 min of perfusion. Increase 200 \times . WIS: Similar to normal rats; SHR: Spontaneously hypertensive rat; WKY: Wistar Kyoto.

Glucose release induced by Ang II or Epi

Following Ang II injection, the amount of glucose released (Figure 2A and B) from the L-NAME group was similar compared to the WIS group, whereas the amount released from SHR livers was lower than its WKY control group

(Table 2).

The glucose release induced by epinephrine is shown in Figure 2C and D; the amount released (AUC) from the L-NAME group (4.2 ± 0.4) was lower when compared to its WIS control group (7.5 ± 0.9), whereas the SHR

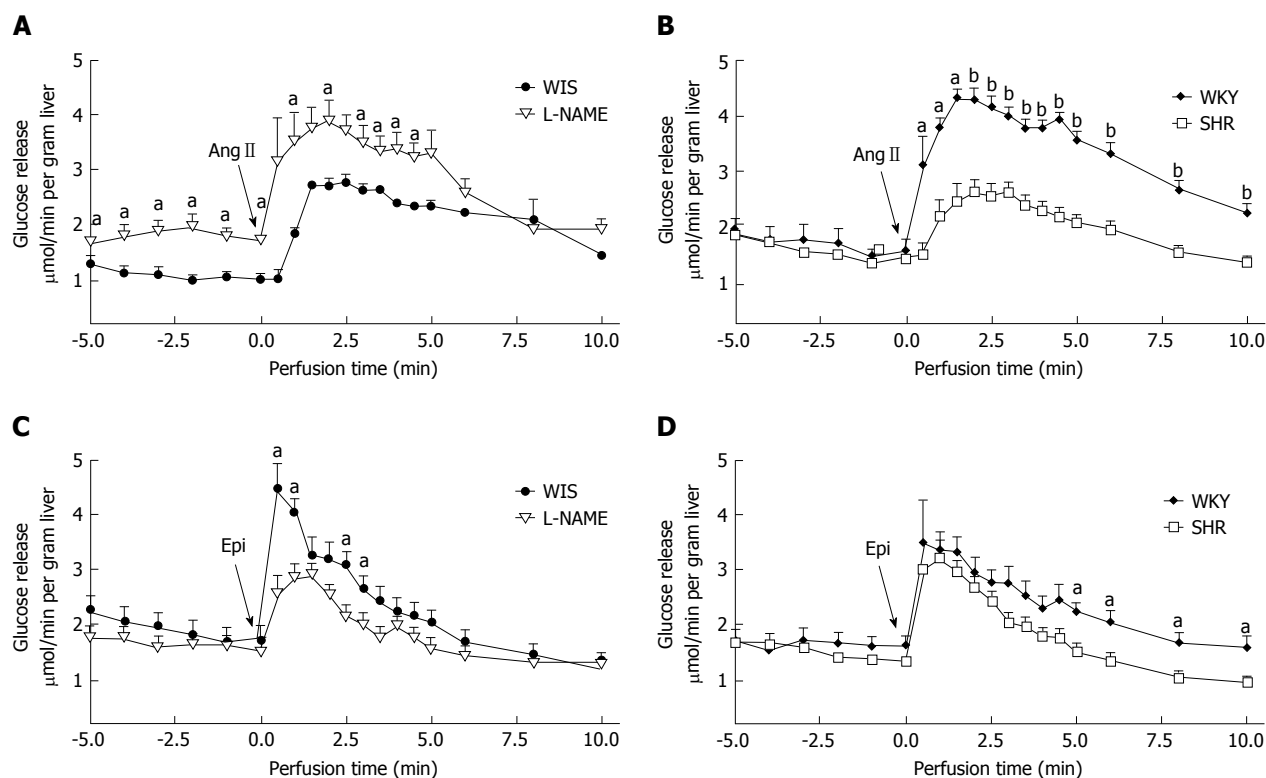


Figure 2 Glucose release induced by angiotensin II and epinephrine. Livers were perfused with Krebs-Henseleit-bicarbonate buffer and after stabilization 2 nmol Ang II (A, B) or 40 nmol Epi (C, D) was injected *in bolus* into afferent cannula and this moment was considered as time 0 min. Glucose release was determined in perfusate aliquots collected during all experiments. Student's *t*-test; ^a*P* < 0.05 and ^b*P* < 0.0001 compared with respective controls for each time point. WIS: Similar to normal rats; SHR: Spontaneously hypertensive rat; WKY: Wistar Kyoto; Ang: Angiotensin; Epi: Epinephrine.

group was similar to the WKY group (Table 2).

PHR to Ang II or Epi

Basal portal pressure (before agonist injection) was similar in all groups. Ang II (2 nmol) or Epi (40 nmol) was injected in portal vein and both agonists promoted portal vasoconstriction. Despite a 20-fold difference in agonists doses, the maximum portal pressure increase (cmH₂O) induced by Ang II and Epi was similar in among groups (Ang II: WIS: 7.9 ± 1.2 , *n* = 7; L-NAME: 7.6 ± 1.1 , *n* = 7; WKY: 10.5 ± 0.3 , *n* = 7; SHR: 6.5 ± 1.2 , *n* = 10; Epi: WIS: 6.1 ± 0.7 , *n* = 10; L-NAME: 8.9 ± 0.7 , *n* = 8; WKY: 7.9 ± 0.7 , *n* = 8; and SHR: 6.2 ± 0.5 , *n* = 6).

The hepatic portal pressure increase after bolus injection of Ang II was normalized after about 10 min of perfusion (Figure 3A and B). The curve profile of portal pressure of L-NAME and SHR groups was similar to their control groups (WIS and WKY, respectively). The PHR induced by Ang II in both L-NAME and SHR was similar when compared to their WIS and WKY control groups, respectively (Table 3). The effect of Epi in portal pressure was more transient than Ang II. Following Epi injection, the portal pressure increase was normalized after about 5 min (Figure 1). The PHR induced by Epi in the L-NAME group was higher when compared to the WIS group. On the other hand, no difference in PHR of SHRs existed compared to the control WKY group (Table 3).

DISCUSSION

All key components of the RAAS are present in the normal liver and are up-regulated in response to chronic liver injury, with growing evidence that the intrahepatic RAAS plays important roles in both the pathophysiology of portal hypertension and liver fibrosis^[18]. The use of ACE/Ang II/AT1R axis inhibitors associated with ACE2/Ang (1-7)/Mas axis activation is a promising strategy-serving regimen to prevent and treat chronic liver diseases as well as acute liver injury^[37]. Hepatic glucose metabolism can be modulated by NO directly inhibiting glycogen synthesis and gluconeogenesis, and indirectly inhibiting glycogen breakdown *via* the secretion of other intrahepatic mediators^[38,39].

In the liver, both Ang II and Epi cause vasoconstriction and glucose release. Although the liver is not considered the target organ in hypertension pathophysiology, it is an important metabolic regulator organ. To study hepatic effects of Ang II and Epi, we used two different experimental models of hypertension: Pharmacological (systemic inhibition of NO synthase) and genetic (SHR). Chronic oral administration of L-NAME promotes a rapid deployment of hypertension in the first days of treatment that is largely mediated by the RAAS. The rats treated with ACE inhibitors, such as captopril and enalapril, or with AT1 receptor antagonists, such as losartan, restore blood pressure to near normal levels^[40,41]. In our study,

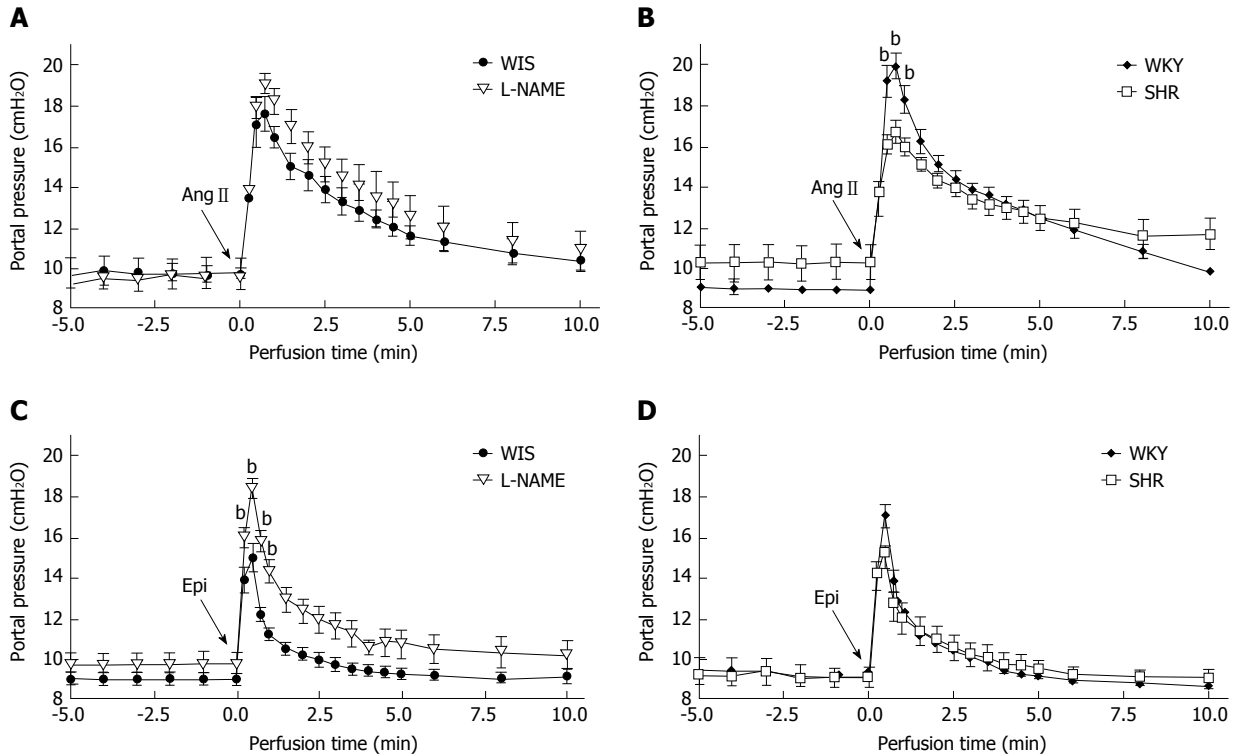


Figure 3 Portal pressure induced by angiotensin II or epinephrine. Livers were perfused with Krebs-Henseleit-bicarbonate buffer and after 20 min stabilization, 2 nmol Ang II (A, B) or 40 nmol epinephrine (C, D) was injected *in bolus* into afferent cannula and this moment was considered as time 0 min. The portal pressure was continuously monitored by water manometer attached to the circuit before the cannula. Student's *t*-test; ^a*P* < 0.0001 compared with respective controls for each time point. WIS: Similar to normal rats; SHR: Spontaneously hypertensive rat; WKY: Wistar Kyoto; Ang: Angiotensin; Epi: Epinephrine.

Table 2 Glucose release induced by angiotensin II or epinephrine

Group	Glucose released $\mu\text{mol}/\text{min}\cdot\text{g liver}$			
	Angiotensin II	<i>n</i>	Epinephrine	<i>n</i>
WIS	11.3 \pm 0.9	7	7.5 \pm 0.9	10
L-NAME	11.2 \pm 1.5	7	4.2 \pm 0.4 ^d	8
WKY	16.4 \pm 1.5	7	8.0 \pm 0.9	8
SHR	5.42 \pm 0.6 ^b	10	5.9 \pm 0.7	6

The amount of glucose (area under the curve) was calculated from the curve glucose release increase *vs* time after agonist injection. Student's *t*-test; ^b*P* < 0.0001 and ^d*P* = 0.002 compared with respective control (L-NAME *vs* WIS and SHR *vs* WKY). WIS: Similar to normal rats; SHR: Spontaneously hypertensive rat; WKY: Wistar Kyoto.

Table 3 Portal hypertensive response to angiotensin II or epinephrine

Group	Portal hypertensive response $\text{cmH}_2\text{O}\cdot\text{min}$			
	Angiotensin II	<i>n</i>	Epinephrine	<i>n</i>
WIS	26.4 \pm 3.2	7	8.2 \pm 0.8	10
L-NAME	38.1 \pm 4.8	7	18.5 \pm 1.9 ^b	8
WKY	29.0 \pm 1.1	7	10.0 \pm 1.1	8
SHR	25.9 \pm 3.7	10	10.5 \pm 1.1	6

The portal hypertensive response (PHR; area under the curve) was calculated from portal pressure increase curve *vs* time after agonist injection and expressed as $\text{cmH}_2\text{O}\cdot\text{min}$. Student's *t*-test; ^b*P* < 0.0001 compared with respective control (L-NAME *vs* WIS and SHR *vs* WKY). WIS: Similar to normal rats; SHR: Spontaneously hypertensive rat; WKY: Wistar Kyoto.

10 d of L-NAME treatment were sufficient to induce a high level systolic blood pressure. On the other hand, the SHR strain is the most widely used phenotypic experimental model in hypertension research with specific potential in the study of polygenic hypertension, being associated with cardiac hypertrophy, heart failure, and renal dysfunction. Hepatic functions are also altered at the molecular level in this model of primary hypertension^[42].

Treatment with L-NAME did not affect fasting glucose levels but reduced significantly insulin levels in blood and increased insulin sensitivity of rats^[43]. Gouveia *et al.*^[44] described increased glycemia and insulinemia values for fasted or fed SHRs. We observed normal glycemia and insulinemia in both hypertension models in fed state, which contrasts with the studies that show changes in

these metabolic parameters. The discrepancy may be due to the metabolic states of the animals in the studies.

Tarsitano *et al.*^[43] described how prolonged treatment (2-8 wk) with NO synthase inhibitor enhanced hepatic glycogen levels. In our study, as the treatment with L-NAME was only for 10 d, the amount of liver glycogen was similar to the WIS group. This short period of treatment might not have been enough to observe possible changes in the glycogen content. Chronic or acute administration of an inhibitor of NO synthesis (L-NAME or L-NNMA) was shown to alter systemic RAAS, decreasing plasma level Ang II as well as renin activity^[45]. Nevertheless, hepatic glucose release profile induced by Ang II in chronically treated L-NAME animals was similar to the control, which suggests that NO is not involved in the glucose release

after induction.

Interestingly, in the L-NAME group, the glucose release induced by Epi was lower than in the control group, suggesting that this effect may be related to the inhibition of NO synthesis. In cultured rat hepatocytes, Hodis *et al.*^[46] observed that glycogenolysis occurs *via* α -adrenergic stimulation and signaling cascade that involves the production of NO. Similarly, our results suggest that the chronic inhibition of NO synthase might inhibit hepatic glycogenolysis, which in turn decreases the release of glucose in the perfusate during the experiment. Therefore, the differences in glucose release following the L-NAME treatment evidenced that the increase in hepatic glycogenolysis was probably mediated by NO when activated by Epi but not by Ang II.

In the SHR group, it was described that muscle glycogen content was lower, but livers presented similar levels of glycogen in the fed and fasted states^[44]. Likewise, we found similar amounts of liver glycogen in the SHR and WKY groups. Despite this similarity, after Ang II *in bolus* injection, glucose released was lower in the SHR group compared to the control group. This result suggests that glucose release is not necessarily related to glycogen content, but may be due to a possible difference in glycogen phosphorylase activation by increased $[Ca^{2+}]_i$ induced by Ang II^[47]. On the contrary, in this hypertension model, glucose release induced by Epi was similar when compared to the control.

Both Ang II and Epi are potent physiological vasoconstrictors. We observed that although these agonists led to similar maximum increases of the portal pressure, Ang II promoted a higher PHR, even using doses 20-fold lower. These response differences may be related to the prolonged responses induced by Ang II in the liver or with the amount of Ang II receptor vs Epi receptor. An enhanced Ang II-mediated vasoconstriction was observed in healthy elderly individuals and this apparent increase is due, at least in part, to the potentiation of α -adrenergic vasoconstriction. These findings suggest that cross-talk between RAAS and adrenergic systems may be an important regulator of resting vascular tone and muscle blood flow with advancing age^[48]. Cross-talk between the α 1-adrenergic receptor (α 1R) and AT1R potentially exists on two levels: Receptor heterodimerization between α 1R and AT1R and second messenger level^[49].

No difference in the PHR of Ang II in the pharmacologic hypertensive model was found, which suggests no changes in the expression of hepatic AT1 receptor. Our result contrasts with AT1R up-regulation described in the L-NAME model in other tissues such as the aorta^[50], adrenals^[51] and heart^[52].

On the other hand, in L-NAME-treated animals, Epi induced increased PHR. It was shown that in rats, chronic inhibition of NO synthase produces endothelial dysfunction, increased vascular response to adrenergic stimulation, and perivascular inflammation^[53]. NO is also involved in regulation of sympathetic nerve activity in human skin and muscle cells^[54]. Therefore, this increased

hypertensive effect in the liver of L-NAME-treated rats may be related to increased sympathetic vascular activity. The disparity between the effects of portal vasoconstriction (higher) and glucose released (lower) in the L-NAME group is a further indication that these effects might be dissociated in two components: One with direct action in the hepatocyte and the other as a presinusoidal response.

We also observed similar vasoconstrictor effect of Ang II in the SHR group. Although in this strain, higher levels of AT1R gene expression was described in brain regions involved in arterial blood pressure control^[55]. Despite widely described sympathetic hyperactivity in this model^[56-58], in this work, PHR to Epi on SHRs was similar to the control group.

In conclusion, Ang II and Epi responses are altered in different ways in these two models of hypertension. Our results suggest that inhibition of NO production seems to be involved in the hepatic hemodynamic and metabolic effects induced by Epi but not by Ang II. Furthermore, diminished glucose release induced by Ang II in SHR is not related to glycogen content, but to the glycogen phosphorylase activation by Ang II, that is under investigation.

COMMENTS

Background

In a normal liver, angiotensin (Ang) I is rapidly converted in Ang II by hepatic angiotensin converting enzyme, and Ang II promotes hypertensive response mediated by the AT1 receptor. Besides this hemodynamic effect, Ang II induces metabolic effects (glucose release and O₂ consumption). Epinephrine promotes hepatic metabolic (glucose and lactate release and O₂ consumption increase) as well as hemodynamic (vasoconstriction) effects. It has also been described as a correlation between the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system; the latter is activated by Ang II and plays a fundamental role in the homeostasis of blood pressure control. In hypertension, sympathetic hyperactivity is described but little is known about this hyperactivity in the liver. The hepatic response to Ang II and Epinephrine in hypertension has not been studied yet. Therefore, the relevance of this study is to understand the hepatic effects of these hormones in two different hypertensive models.

Research frontiers

The RAAS and the catecholaminergic system are present in the normal liver. The interaction of RAAS with the catecholaminergic sympathetic nervous system in the liver of hypertensive animals might bring to light relevant aspects of the relationship among metabolic disorders such as hypertension, type II diabetes, obesity, and hypertriglyceridemia.

Innovations and breakthroughs

No description of hemodynamic and metabolic effects of the two hormones Ang II and Epi exists in the literature on RAAS and the catecholaminergic system in the livers of hypertensive rats. This is the first study evaluating hemodynamic and metabolic effects of the two hormones Ang II and Epi. Inhibition of NO production in the L-NAME model increased hepatic hemodynamic and metabolic effects induced by Epi but not by Ang II. Furthermore, diminished glucose release induced by Ang II in SHRs is not related to glycogen content. Therefore, the hepatic effect of Ang II or Epi is different depending on the pathophysiology of systemic arterial hypertension.

Applications

Although not target organs in hypertension, RAAS and sympathetic nervous system are overexpressed, elucidating the hepatic role of these systems, which

can bring knowledge about metabolic-related comorbidities and therapeutics.

Terminology

The portal hypertensive response represents the area under the curve and was calculated from the graphic: Portal pressure increase (cmH₂O) vs time after agonist injection (min) and expressed as cmH₂O.min. It considers not only the perfusion pressure increase but the effect of the agonist over time.

Peer-review

In this paper, authors give some new information about the effects of Epi and Ang II on glucose release, finding that inhibition of NO production seems to be involved in the hepatic hemodynamic and metabolic effects induced by Epi but not by Ang II.

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